Remarks

I. Support for Amendments

Claims 1-18 are pending in this application. Claims 1, 4, 5, 8 and 9 have been amended herein. Claim 1 has been amended to more clearly define the invention and to incorporate the steps of claims 2, 3 and 6. Claims 4, 5, 8 and 9 have been amended to more clearly define the invention. Support for these amendments can be found throughout the specification, for example, on page 7 lines 13 -15 and 29, page 25 line 30, page 28 lines 1 and 29-33, page 29 line 5, page 34 line 6, Example 4 on page 38 and Example 5 on page 40. Accordingly, claims 2, 3 and 6 have been canceled herein without prejudice or disclaimer of the subject matter claimed therein. In addition, dependent claims 4 and 7 have been amended to correct their dependency. Accordingly, no new matter has been added by this amendment and entry thereof is respectfully requested. The outstanding rejections are addressed individually below.

II. Rejection of Claims 1-17 Under 35 U.S.C. § 112, second paragraph

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

Applicants respectfully traverse this rejection. Claim 1, as amended, recites the specific method steps of "providing a first fusion polypeptide comprising an immunoglobulin fused to a first molecule" and "providing a second fusion polypeptide comprising a target fused to a second molecule, wherein said first and second molecules are separable domains of a reporter molecule." In addition, claim 1 has been amended herein to recite the steps of "expressing said first fusion polypeptide together with said second fusion polypeptide in an intracellular environment, wherein the binding of said immunoglobulin with said target brings said first molecule and said second molecule into operative association to produce a detectable reporter molecule" and "detecting said detectable reporter molecule, wherein said detection is indicative of binding between said immunoglobulin and said target in an intracellular environment." Support for these amendments can be found, *inter alia*, in the specification on page 5 line 16, page 6 line 30, page 7 lines 13-15 and 29, page 25 line 30, page 27 line 29, page 28 lines 1 and

10, page 34 line 32, page 37 line 16 and 29-33, page 29 line 5, page 34 line 6, Example 4 on page 38 and Example 5 on page 40.

Applicants respectfully submit that claim 1, as amended, provides clear and definite steps. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

III. Rejection of Claims 1-17 Under 35 U.S.C. § 112, first paragraph

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement. Specifically, the Examiner asserts that the specification does not appear to provide any literal or descriptive support for the recitation of "unknown immunoglobulins."

Applicants respectfully traverse this rejection. Claim 1 has been amended to remove the recitation "unknown." Accordingly, Applicants respectfully submit that this rejection has been overcome and request that this § 112, first paragraph, rejection be reconsidered and withdrawn.

IV. Rejection of Claims 1-17 Under 35 U.S.C. § 102(b)

Claims 1 to 17 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Gargano *et al.* Applicants respectfully submit that the claims, as amended, are neither anticipated nor rendered obvious by Gargano *et al.*

Claim 1 has been amended to recite, "wherein said immunoglobulin was subjected to no more than one preselection step," as described in the specification, for example, in Examples 4 and 5. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Gargano *et al.* teach that the size of the antibody repertoire derived from a phage display library is too large to test in a selection system *in vivo* (such as yeast two hybrid) and that preselection steps (such as affinity purification on an antigen column) are needed to first enrich the population for phages that are able to bind the antigen of interest *in vitro*. Moreover, Gargano *et al.* teach that each successive cycle or step of preselection further enriches the pool of affinity purifed scFv fragments (see page 174, end of 3rd paragraph, page 176, 2nd full paragraph, page 177, 4th full paragraph, page 183, 1st paragraph, page 185, 1st paragraph and Figure 10.2).

While Gargano *et al.* teach that several preselection steps are required, the instant application discloses "screening of entire antibody libraries, such as phage libraries, without prior application of phage display to isolate the antibodies which bind to the desired antigen" (see page 28, lines 29-33, Example 4 on page 38 and Example 5 on page 40). Applicants show that subjecting the phage library to only one round of preselection will enrich the population for antibodies which bind to the desired antigen in an intracellular environment (see Example 5), but also disclose that direct selection of scFv libraries in a yeast antibody-antigen system, without any preselection to reduce the size of the library, is feasible (see Example 4).

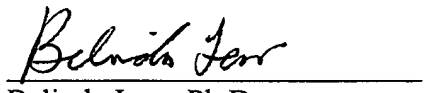
Furthermore, Applicants enclose herewith Visintin *et al.* (Appendix A), the co-authors of which include two (Drs. Visintin and Cattaneo) of the four co-inventors, and which extends the experiments described in the instant application, and discloses that "performing **only one** round of enrichment *in vitro*, prior to the selection in yeast, yields a more complete repertoire of ICAbs (intracellular antibodies)" (see page 75, 1st paragraph and Table 1). It is submitted that Visintin *et al.*, published after the priority date of the instant application, confirms that, contrary to teachings of the art, many preselection steps are not only irrelevant, but also counterproductive, for efficient rescue of genuine intracellular antibodies.

Thus, Gargano *et al.*, which does not teach subjecting the immunoglobulin to at most one preselection step, does not teach every element of the claimed invention and therefore, does not anticipate claims 1-17 as amended. Accordingly, withdrawal of the rejection of claims 1-17 under 35 U.S.C. § 102(b) over Gargano *et al.* is respectfully requested.

V. Conclusion

In view of the foregoing remarks, Applicants believe that the application is in condition for allowance. However, if the Examiner disagrees, the Examiner is encouraged to call the undersigned at the number listed below in order to expedite the prosecution of this application.

Respectfully submitted,



Belinda Lew, Ph.D.
Agent for Applicants
Registration No. 53,212

Date: March 21, 2007
WILMER CUTLER PICKERING HALE AND DORR LLP
1875 Pennsylvania Ave., NW
Washington, DC 20006
Tel: (202) 663-6000
Fax: (202) 663-6363